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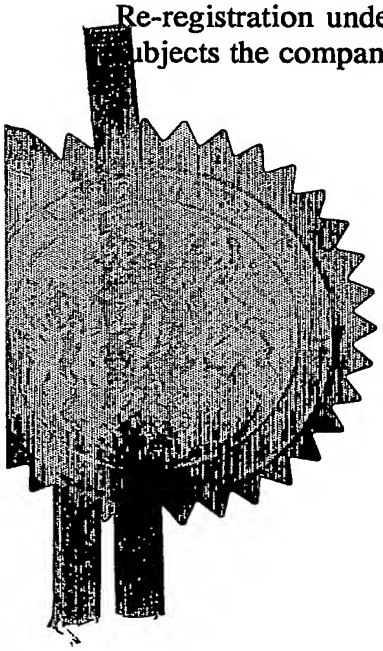

Signed Stephen Hordley

Dated 24 March 2003

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THE PATENT OFFICE
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

20 MAY 2002

The Patent Office
Cardiff Road
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NP10 8QQ

1. Your reference

HL 82196/000

2. Patent application number
(The Patent Office will fill in this)

0211529.3

21MAY02 E719938-1 002847
P01/7700 0.00-0211529.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

First Water Limited
Hilldrop Lane, Ramsbury,
Malborough, Wiltshire. SN8 2RB

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

7358625001

4. Title of the invention

IONIC HYDROGELS WITH LOW AQUEOUS FLUID ABSORPTION

5. Name of your agent *(if you have one)*

Haseltine Lake

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Imperial House
15-19 Kingsway
London
WC2B 6UD

Patents ADP number *(if you know it)*

34001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

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Description	6 ✓ w-
Claim *(s)*	0
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Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 20/5/02.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. David Nash [0117] 910 3200

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IONIC HYDROGELS WITH LOW AQUEOUS FLUID ABSORPTION

FIELD OF THE INVENTION

The present invention relates to polymeric hydrogels, and more particularly to cross-linked polymeric hydrogels for contacting mammalian body tissue, e.g. skin or flesh. Such hydrogels may, for example, be used in association with patches for cosmetic devices, sensing electrodes, stimulation electrodes, devices for iontophoretic delivery of active agents, passive drug delivery devices, wound dressings, foot dressings, fixation aids for human incontinence devices, medical devices, for example catheters, cannulas, ostomy bags and prosthetics, for example breasts and limbs.

BACKGROUND OF THE INVENTION

Cross-linked conductive polymeric hydrogels have been used in medical devices, such as biomedical electrodes, to adhere the device to mammalian skin, to provide a secure conductive connection between the device and the skin for stimulation or sensing purposes. Most known compositions are based on polymeric matrices that are ionic in nature. Similar compositions are also known generally to be useful as wound dressings. The presence of the ionic groups imparts polyelectrolyte behaviour to the hydrogel. However, in certain applications, the known hydrogel compositions possessing polyelectrolyte character have been found to have significant disadvantages.

U.S. Patent No. 3,929,741 (the disclosure of which is incorporated herein by reference) discloses anionic hydrogels based on 2-acrylamido-2-methylpropane sulphonic acid (AMPS) and its salts for use in contact lenses and wound dressings.

U.S. Patent No. 4,391,278 (the disclosure of which is incorporated herein by reference) discloses anionic hydrogels based on 2-acrylamido-2-methylpropane sulphonic acid (AMPS) and its salts for use in biomedical electrodes.

U.S. Patent No. 5,800,685 (the disclosure of which is incorporated herein by reference) discloses cationic hydrogels based on acrylic esters of quaternary chlorides or sulphates or acrylic amides of quaternary chlorides for use in biomedical electrodes. Copolymers of cationic and anionic monomers are mentioned generally, but not exemplified. The hydrogels are disclosed to be polyelectrolytes.

The gels disclosed in the above publications are considered to possess generally polyelectrolyte behaviour. Gels that are polyelectrolytes can potentially absorb significant quantities of aqueous solution and can then lose their as-made structural integrity and hence their usefulness. In mammalian skin contact applications the aqueous fluid may for example arise from sweat, exudates from wounds and bathing media.

WO-A-91/15250 (the disclosure of which is incorporated herein by reference) discloses amphoteric hydrogels formed from the copolymerisation of monomers possessing pendant strong acid groups, for example sulphonic acid, with monomers possessing pendant groups which are salts of strong basic groups, for example quaternary ammonium salts where at least one of the monomers is an N-substituted

acrylamide. Many of the gels exemplified would be expected to exhibit polyampholytic characteristics as a consequence of global ionic balance. In the one example where the monomer with the pendant sulphonic acid is present as a salt, the resulting hydrogel is not ionically balanced and hence would be expected to exhibit polyelectrolyte behaviour.

U.S. Patent No. 5,846,558 (the disclosure of which is incorporated herein by reference) discloses hydrogels based on polymers and copolymers of zwitterionic monomers. The anion and cation are carried on the same molecule in these monomers. No disclosure is made of any uptake of aqueous fluids.

It is an object of the present invention to provide ionic polymeric hydrogels possessing at least some resistance to the uptake of aqueous fluids possessing from zero to high ionic strength.

It is a further object of the present invention to provide ionic hydrogels exhibiting relatively low absorption of aqueous fluids and also relatively high moisture vapour transmission rates.

It is a further object of the present invention to provide ionic polymeric hydrogel adhesives that can be used in diverse applications, for example medical devices including biomedical electrodes, ostomy, incontinence devices, skin contact devices for the delivery of medicaments, footcare and prosthetics.

It is a further object of the present invention to provide polymeric hydrogels with low aqueous fluid uptake in the form of films, more preferably a significantly reduced aqueous fluid uptake in comparison with known polymeric hydrogel films.

It is a further object of the present invention to provide polymeric hydrogels with significantly reduced aqueous fluid uptake in the form of foams and foam/film composites, in comparison with known polymeric hydrogels in the form of foams and foam/film composites.

SUMMARY OF THE INVENTION

According to the present invention, we provide a cross-linked polymeric hydrogel suitable for use in mammalian body tissue (e.g. skin) contacting applications, which comprises a cross-linked copolymer formed from a first monomer comprising one or more pendant anionic group and a second monomer comprising one or more pendant cationic group, the relative amounts of the said monomers in the copolymer being such that the anionic groups and cationic groups are present in essentially equimolar quantities.

In one embodiment, the said anionic and cationic groups may be selected from groups which are salts of acid groups and groups which are salts of basic groups.

It is preferred that the copolymer is formed by the simultaneous crosslinking and copolymerising of the monomers, in suitable amounts whereby the molar ratio of anionic to cationic groups in the copolymer is substantially unity.

We have found that acceptable ionic mobility is present in the hydrogels according to the present invention, without the need for additional ions (e.g. ions from salts introduced into the polymerisation reaction mixture or the hydrogel) to impart this property. Additional ingredients may also be present in the hydrogel composition according to the present invention. Such additional ingredients may, for example, include one or more ionic and/or non-ionic compounds, such as medicaments (for example: antiseptics, antimicrobial agents, antibiotics, analgesics, anaesthetics), humectants (for example: glycerol, sorbitol, polyethylene glycol, methyl ether terminated polyethylene glycol), vitamins, adhesion enhancers (for example: vinyl acetate dioctylmaleate copolymers), pH buffers, citric acid, salicylic acid, surfactants and water soluble polymers (for example: polysaccharides and synthetic polymers).

The pendant groups in the first monomer are preferably the sodium, potassium, calcium, lithium and/or ammonium (individually or in any combination of one or more) salts of carboxylic acid, phosphoric acid and/or sulphonic acid. Sulphonic acid groups are most preferred. The pendant groups in the second monomer are preferably quaternary ammonium salts of halide (for example chloride), sulphate and/or hydroxide. Chloride and sulphate are most preferred.

The hydrogels of the present invention can suitably be made in aqueous solution by polymerisation of the first and second monomers, optionally with additional monomers. The nature and proportions of any such additional monomers should be such that the polyampholytic characteristics of the final hydrogel, deriving from the substantially equimolar amounts of anionic and cationic monomers, are not substantially disrupted. Non-limiting examples of suitable additional monomers include hydroxyethyl acrylate and methacrylate, acryloyl morpholine, vinyl pyrrolidone, polyethylene acrylates and methacrylates, acrylamide and N-substituted acrylamides and soya bean epoxy acrylate and any combination thereof. Further examples of suitable additional non-ionic monomers also include di-, tri-, and multi functional crosslinking agents, for example polyethylene glycol diacrylate (molecular weight between about 100 and 10,000) and methylene bisacrylamide, and mixtures thereof.

Simultaneously cross-linking and polymerising the monomers in aqueous solution by conventional free radical polymerisation utilising appropriate polymerisation catalysts can make the hydrogels of the present invention. Such free radical polymerisation may be initiated by any suitable initiation method, for example thermal, redox, ultra-violet light, gamma irradiation and electron beam initiation, which methods are known by those skilled in the art. Ultra-violet light initiated polymerisation is the preferred method. The polymerisation mixture preferably includes appropriate amounts of one or more initiator to assist the initiation process.

The hydrogels of the present invention can be made by initially depositing the uncured pregel mixture, preferably as a layer, e.g. by casting onto a suitable member, such as a porous or non-porous film, net or non-woven material which are suitably made from synthetic materials, natural materials or mixtures of both. The deposited pregel may suitably be in the form of a continuous film, or as islands, or as a foam layer or body. The cured hydrogels can also be made to encapsulate porous materials such as non-wovens and nets.

DETAILED DESCRIPTION OF THE PREFFERED EMBODIMENTS

As is set forth above the present invention relates to conductive and adhesive hydrogels for use in a variety of applications involving contact with mammalian skin. These hydrogels possess a significantly reduced aqueous fluid uptake compared to those previously known in the art. The anionic monomer is preferably the sodium or potassium salt of 3-sulphapropyl acrylate (SPA) or the sodium or potassium salt of 2-acrylamido-2-methylpropane sulphonic acid or a mixture of both. The cationic monomer is preferably either a quaternary ammonium salt derivative of acrylic acid or a quaternary ammonium salt derivative of an N-substituted acrylamide or combinations of both. Preferred examples include acryloyloxyethyltrimethyl ammonium chloride (DMAEA-Q, Kohjin), acryloyloxyethyltrimethyl ammonium methyl sulphate (Aldrich), acrylamidopropyltrimethyl ammonium chloride (Kohjin).

The total amount of ionic monomer present in the hydrogel pre-polymerisation mix for making a film is about 1-60%, preferably about 10-45%, preferably about 20-45% by weight of the total composition, such that the molar ratio of anionic to cationic monomer is preferably from about 0.8 to about 1.2, preferably about 0.9 to about 1.1, preferably about 0.95 to about 1.05 and more preferably about 1. The balance of the composition comprises water, preferably about 10 to about 80%, preferably about 15 to about 40%, a polyhydric alcohol 0 to about 50%, preferably about 10 to about 40%, where the polyhydric alcohol is preferably glycerol (Aldrich), a cross-linking agent about 0.04% to about 2 % preferably about 0.06 to about 0.3%, where the preferred crosslinking agent is polyethylene glycol diacrylate (Aldrich), a photoinitiator (Darocure 1173 or Irgacure 184 or combinations of both) preferably about 0.001% to about 0.1% and additional additives for example medicaments, adhesion promoters, 0% to about 10% .

The total amount of ionic monomer present in the hydrogel pre polymerisation mix for making a foam is about 1-60%, preferably about 10-45%, preferably about 20-45% by weight of the total composition, such that the molar ratio of anionic to cationic monomer is preferably from about 0.8 to about 1.2, preferably about 0.9 to about 1.1, preferably about 0.95 to about 1.05 and more preferably about 1. The balance of the composition comprises water, preferably about 10 to about 80%, preferably about 15 to about 40%, a polyhydric alcohol 0 to about 50%, preferably about 10 to about 40%, where the polyhydric alcohol is preferably glycerol (Aldrich), a cross-linking agent about 0.04% to about 2 % preferably about 0.06 to about 0.3%, where the preferred crosslinking agent is polyethylene glycol diacrylate (Aldrich), a photoinitiator (Darocure 1173 or Irgacure 184 or combinations of both) preferably about 0.001% to about 0.1%, surfactant about 0.001% to about 10% where the surfactant is preferably non ionic, for example a Pluronic from Ciba Geigy(P65, L64) and additional additives for example medicaments, adhesion promoters, 0% to about 10% .

In one embodiment, the hydrogel compositions according to the present invention consist essentially of the defined cross-linked copolymer according to the general definition of the invention stated above in the Summary of the Invention, together with one or more of water, and optionally one or more of a surfactant and a humectant (e.g. a polyhydric alcohol), with less than about 10%, more typically less than about 8%, more preferably less than about 5%, of other ingredients such as one or more of

medicaments and adhesion promoters. The proportions of the ingredients are preferably as stated above.

All percentages of ingredients are given by weight.

From the assembly of the prepolymerisation mix, a continuous film is preferably made by coating the mix onto a substrate, preferably siliconised for easy release, such as polyester, polyethylene, polypropylene, polyurethane, paper or a net, foam or a non woven material made from natural and/or synthetic materials, and passed under a UV light for curing. After curing a siliconised cover is placed on top of the exposed surface of the hydrogel. The thickness of the hydrogel film can be from about 0.05mm to about 3mm.

A foamed hydrogel of the present invention can suitably be made by mechanically agitating the premix and then coating on to web as for the film. The foam so formed can be porous throughout its thickness, or can be coated such that a composite structure of film supporting a foam can be made. The thickness of the foam or film foam structure can suitably be from about 0.1mm to about 3mm.

EXAMPLES

1. 40.84g of a 58% aqueous solution of NaAMPS (Lubrizol) were mixed with 25g of a 79% aqueous solution of DMAEA-Q (Kohjin) and 34.16g of Glycerol for 30 minutes. To this mixture 0.19g of a Darocure 1173 photoinitiator (4 parts) and polyethylene glycol diacrylate (IRR 280, UCB) (20 parts) solution was added and stirred for 30 minutes. The mixture was then coated on to a siliconised polyester backing and passed under a UV lamp. The mixture cured rapidly to produce a gel with good tack and adhesion properties. The gel had low saline uptake.

2. 2. 20.42g of a 58% aqueous solution of NaAMPS (Lubrizol) and 20.44g of a 58% aqueous solution of SPA (potassium salt) (Raschig) were mixed with 25g of a 79% aqueous solution of DMAEA-Q (Kohjin) and 34.16g of Glycerol for 30 minutes. To this mixture 0.19g of a Darocure 1173 photoinitiator (4 parts) and polyethylene glycol diacrylate (IRR 280, UCB) (20 parts) solution was added and stirred for 30 minutes. The mixture was then coated on to a siliconised polyester backing and passed under a UV lamp. The mixture cured rapidly to produce a gel with good tack and adhesion properties. The gel had low saline uptake.

3. 20.42g of a 58% aqueous solution of NaAMPS (Lubrizol) were mixed with 12.5g of a 79% aqueous solution of DMAEA-Q (Kohjin) and 67.08 of Glycerol for 30 minutes. To this mixture 0.25g of a Darocure 1173 photoinitiator (4 parts) and polyethylene glycol diacrylate (IRR 280, UCB) (20 parts) solution was added and stirred for 30 minutes. The mixture was then coated on to a siliconised polyester backing and passed under a UV lamp. The mixture cured rapidly to produce a gel with good tack and adhesion properties. The gel had low saline uptake.

4. 40.84g of a 58% aqueous solution of SPA (potassium salt) (Raschig) were mixed with 25g of a 79% aqueous solution of DMAEA-Q (Kohjin) and 34.16g of Glycerol for 30 minutes. To this mixture 0.19g of a Darocure 1173 photoinitiator (4 parts) and polyethylene glycol diacrylate (IRR 280, UCB) (20 parts) solution was

added and stirred for 30 minutes. The mixture was then coated on to a siliconised polyester backing and passed under a UV lamp. The mixture cured rapidly to produce a gel with good tack and adhesion properties. The gel had low saline uptake.

5. 40.84g of a 58% aqueous solution of NaAMPS (Lubrizol) were mixed with 25g of a 79% aqueous solution of DMAEA-Q (Kohjin) and 34.16g of Glycerol for 30 minutes and 3g of Pluronic P65 (Ciba Geigy). To this mixture 0.19g of a Darocure 1173 photoinitiator (4 parts) and polyethylene glycol diacrylate (IRR 280, UCB) (20 parts) solution was added and stirred for 30 minutes. The mixture was mechanically agitated to produce foamed liquid and then coated on to a siliconised polyester backing and passed under a UV lamp. The mixture cured rapidly to produce a gel with good tack and adhesion properties. The gel had low saline uptake compared to gel made using the same method but replacing the DMAEA-Q with NaAMPS.